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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

99810869.0

PRIORITY DOCUMENT

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
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Pharmaceutically Active Sulfonamide Derivatives

Field of the invention

The present invention is related to sulfonamide derivatives for use as pharmaceutically active compounds, as well as pharmaceutical formulations containing such sulfonamide derivatives. In particular, the present invention is related to sulfonamide derivatives displaying a substantial inhibitory activity of the JNK pathway and which are therefore particularly useful in the treatment of disorders of the autoimmune and the neuronal system. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation.

Background of the invention

Apoptosis denotes the complex contortions of the membrane and organelles of a cell as it undergoes the process of programmed cell death. During said process, the cell activates an intrinsic suicide program and systematically destroys itself. The following series of events can be observed :

- The cell surface begins to bleb and expresses pro-phagocytic signals. The whole apoptotic cell then fragments into membrane-bound vesicles that are rapidly and neatly disposed of by phagocytosis, so that there is minimal damage to the surrounding tissue.
- The cell then separates from its neighbors.

The nucleus also goes through a characteristic pattern of morphological changes as it commits genetic suicide, the chromatin condenses and is specifically cleaved to fragments of DNA.

Neuronal cell death plays an important role in ensuring that the nervous system develops normally. It appears that the death of developing neurones depends on the size of the target that they innervate: cells with fewer synaptic partners are more likely to die than those that have formed multiple synapses. This may reflect a process, which balances the relative number of pre- to postsynaptic neurones in the developing nervous system. Although neuronal cell death was assumed to be apoptotic, it was only recently

that neurones in developing rodent brain were conclusively shown to undergo apoptosis as classified by morphology and DNA fragmentation. As cell death during development is clearly not a pathological process, it makes sense that cells actually cease to exist.

Neuronal death occurs via either apoptotic or necrotic processes following traumatic nerve injury or during neurodegenerative diseases. Multiple components are emerging as key players having a role in driving neuronal programmed cell death. Amongst the components leading to neuronal apoptosis are members of the SAPK/JNK being a sub-family of MAP Kinases (MAPKs).

MAPKs (mitogen-activated protein kinases) are serine/threonine kinases that are activated by dual phosphorylation on threonine and tyrosine residues. In mammalian cells, there are at least three separate but parallel pathways that convey information generated by extra-cellular stimuli to the MAPKs. Said pathways consist of kinase cascades leading to activa-tion of the ERKs (extracellular regulated kinases), the JNKs (c-Jun N-terminal kinases), and the p38/CSBP kinases. While both the JNK and p38 pathways are involved in relaying stress-type extramolecular signals, the ERK pathway is primarily responsible for transducing mitogenic/differentiation signals to the cell nucleus.

SAPK cascades represent a sub-family of the mitogen-activating protein kinase family, that are activated by different external stimuli including DNA damage following UV irradia-tion, TNF-α , IL-1β , ceramide, cellular stress, and reactive oxygen species and have dis-tinct substrate specificities. Signal transduction via MKK4/JNK of MKK3/p38 results in the phosphorylation of inducible transcription factors, c-Jun and ATF2, which then act as either homodimers or heterodimers to initiate transcription of down-stream effectors.

c-Jun is a protein that is forming homodimers and heterodimers (with e.g. c-Fos) to produce the transactivating complex AP-which is required for the activation of many genes (e.g. matrix metalloproteinases) involved in the inflammatory response. The JNKs were discovered when it was found that several different stimuli such as UV light and TNF-α stimulated phosphorylation of c-Jun on specific serine residues in the N-terminus of the protein.

In a recent publication of Xie X et al, (*Structure* **1998**, *6 (8)*; 983-991) it has been suggested that activation of stress-activated signal transduction pathways are required for neuronal apoptosis induced by NGF withdrawal in rat PC-12 and superior cervical ganglia (SCG) sympathetic neuronal cells. Inhibition of specific kinases, namely MAP kinase kinase 3 (MKK3) and MAP kinase kinase 4 (MKK4), or c-Jun (part of the MKK-4 cascade) may be sufficient to block apoptosis (see also Kumagae Y et al, in *Brain Res Mol Brain Res*, **1999**, *67(1)*, 10-17 and Yang DD et al in *Nature*, **1997**, *389 (6653)*; 865-870). Within a few hours of NGF deprivation in SCG neurones, c-Jun becomes highly phosphorylated and protein levels increase. Similarly in rat PC-12 cells deprived of NGF, JNK and p38 undergo sustained activation while ERKs are inhibited. Consistent with this JNK3 KO mice are resistant to excitotoxicity induced apoptosis in the hippocampus and more importantly they display greatly reduced epileptic like seizures in response to excitotoxicity as compared to normal animals (*Nature* **1997**, *389*, 865-870).

More recently, it has been reported that the JNK signalling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases (*Immunity*, **1998**, *9*, 575-585; *Current Biology*, **1999**, *3*, 116-125) which are mediated by T-cell activation and proliferation.

Naive (precursor) $CD4^+$ helper T (Th) cells recognise specific MHC-peptide complexes on antigen-presenting cells (APC) via the T-cell receptor (TCR) complex. In addition to the TCT-mediated signal, a costimulatory signal is provided at least partially by the ligation of CD28 expressed on T-cells with B7 proteins on APC. The combination of these two signals induces T-cell clonal expression.

After 4-5 days of proliferation, precursor of $CD4^+$ T cells differentiate into armed effector Th cells that mediate the functions of the immune system. During the differentiation process, substantial reprogramming of gene expression occurs.

Two subsets of effector Th cells have been defined on the basis of their distinct cytokine secretion pattern and their immunomodulatory effects: Th1 cells produce IFNγ and LT (TNF-β), which are required for cell-mediated inflammatory reactions; Th2 cells secrete IL-4, IL-5, IL-6, IL-10 and IL-13, which mediate B cell activation and differentiation. These cells play a central role in the immune response. The JNK MAP Kinase pathway

is induced in Th1 but not in Th2 effector cells upon antigen stimulation. Furthermore, the differen-tiation of precursor $CD4^+$ T cells into effector Th1 but not Th2 cells is impaired in JNK2-deficient mice. Therefore, in recent years it has been realized that the JNK kinase pathway plays an important role in the balance of Th1 and Th2 immune response through JNK2.

With the objective of inhibiting the JNK kinase pathway, WO/9849188 teaches the use of a human polypeptide, i.e. JNK-interacting protein 1 (JIP-1), which is a biological product and which has also been assayed for overcoming apoptosis related disorders.

Although such human polypeptides have been confirmed to have an inhibitory effect onto the JNK kinase pathway, a whole variety of drawbacks are associated with their use :

- Active bio-peptides or bio-proteins are only obtained by means of rather comprehensive and expensive bio-synthesis which consequently frequently renders the resulting products fairly cost-intensive.
- The peptides are known to display poor membrane penetration and may not cross the blood brain membrane,
- Furthermore, their bio-availability is usually rather restricted as notably the oral administration is not available because of decomposition through hydrolysis of said peptides within the acid medium of the stomach, their half-life is substantially restricted by digestion for instance due to the intestinal presence of proteases and, finally,
- in view of the crucial tolerance of administered products, it is a general concern that bio-peptides or bio-proteins are frequently viewed by the host body as intruding material to be disposed of, thus setting off an anti-body response.

Notably the bothersome problems arising from the emergence of diverse anti-body responses is frequently rather difficult to overcome and poses a major inconvenient to the peptide or protein approach.

Hence, it was an objective of the present invention to provide relatively small molecules that avoid essentially all of the above-mentioned drawbacks arising from the use of bio-peptides or bio-proteins, however, which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders. It was notably an objective of the present invention to provide relatively small molecule che-

mical compounds being able to modulate, preferably to inhibit the JNK kinase pathway so to be available as a convenient method of treating a host of diseases. Moreover, it was an objective of the present invention to provide methods for preparing said small molecule chemical compounds. It was furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of a host of diseases. It was finally an objective of the present invention to provide a method of treating diseases that are caused by disorders of the autoimmune and/or the neuronal system.

Description of the invention

The aforementioned objectives have been met according to the independent claims. Preferred embodiments are set out within the dependent claims which are annexed herewith.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

"C_1-C_6-alkyl" refers to monovalent alkyl groups having 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl and the like.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl and the like.

"Heteroaryl" refers to a monocyclic heteromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl,

benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrehydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

"Alkenyl" refers to alkenyl groups preferable having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-$CH=CH_2$), n-propenyl (-$CH_2CH=CH_2$) and the like.

"Alkynyl" refers to alkynyl groups preferably having 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-$C\equiv CH$), propargyl (-$CH_2C\equiv CH$), and the like.

"Acetoxy" refers to the group –OC(O)R where R includes C_1-C_6-alkyl, aryl or heteroaryl.

"Alkoxy" refers to the group "C_1-C_6-alkyl-O-" or "-O-aryl" or "O-heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

"Alkoxycarbonyl" refers to the group –C(O)OR where R includes "C_1-C_6-alkyl" or "aryl" or "heteroaryl".

"Aminocarbonyl" refers to the group –C(O)NRR' where each R, R' includes independently hydrogen or C_1-C_6-alkyl or aryl or heteroaryl.

"Aminoacyl" refers to the group –NR(CO)R' where each R, R' is independently hydrogen or C_1-C_6-alkyl or aryl or heteroaryl.

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Sulfonyl" refers to group "R-SO_2" wherein R is selected from H, aryl, heteroaryl, C_1-C_6-alkyl, C_1-C_6-alkyl substituted with halogens e.g. a CF_3-SO_2 group.

"Sulfoxy" refers to a group "R-S(=O)-" wherein R is selected from H, C_1-C_6-alkyl, C_1-C_6-alkyl substituted with halogens e.g. a CF_3-SO- group, aryl, heteroaryl.

"Thioalkoxy" refers to groups "C_1-C_6-alkyl-S-", or "aryl-S-" or "heteroaryl-S-". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

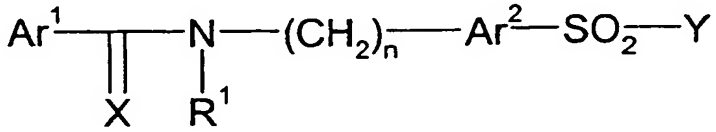
"Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like alkyl, heteroaryl, alkenyl, alkynyl and aryl etc. groups can optionally be substituted with from 1 to 5 substituents selected from group consisting of C_1-C_6-alkyl, acetoxy, alkoxy, alkenyl, alkynyl, amino, aminoacyl, aminocarbonyl, alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfoxy, thioalkoxy, trihalomethyl and the like.

"Pharmaceutically acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the below-identified compounds of formula I and exhibit minor or no undesired toxicological effects. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and polygalacturonic acid. Said compounds can also be administered as pharmaceutically acceptable quaternary salts known by a person skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR,R',R''^{+}Z^{-}$, wherein R, R', R" is independently hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsul-fonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, and diphenylacetate).

"Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

Quite surprisingly, it was now found that sulfonamide derivatives according to formula I are suitable pharmaceutically active agents, by effectively inhibiting the action of JNK's, notably of JNK 2 and 3. In terms of application convenience, the inventively found compounds display a marked superiority compared to the above mentioned pep-

tide or protein approach as they also accessible to oral administration. They could be prescribed by a physician and require only minor supervision. Also, the inventively found compounds are available at lower costs compared to said peptide compounds described hitherto.



I

The compounds of formula I according to the present invention being suitable pharmaceutical agents are those wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

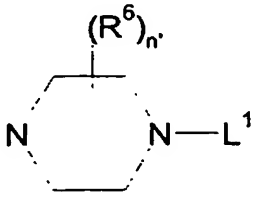
X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, preferably H, or R^1 forms a substituted or unsubstituted 5-6—membered saturated or non-saturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1.

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing the sulfonamide.

In a preferred embodiment of the present invention, Y is either a piperidine or piperazine derivative according to the below formula



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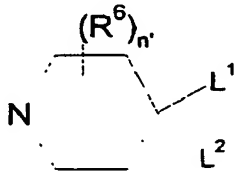


In said piperidine or piperazine groups, L^1 and L^2 are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-

alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$.

Thereby, R^3 and $R^{3'}$ are substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), sulfoxy, acetoxy, thioalkoxy and n' is an integer from 0 to 4, preferably 1 or 2.

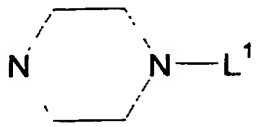
All of the above mentioned aryl or heteroaryl groups could optionally be substituted by at least one of the groups selected from substituted or unsubstituted C_1-C_6-alkyl,like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, acetoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, aminoacyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C_1-C_6-thioalkoxy.

Also L^1 and L^2 taken together could form a 4-8-membered saturated cyclic alkyl or heteroalkyl group, like triazolines, tetrazolines, oxazolines, isoxazolines, oxazoles or isoxazoles. In a preferred embodiment L^1 and L^2 form together 5-6-membered saturated cyclic alkyl ring containing 2-3 nitrogen atoms.

The present invention also includes the geometrical isomers, the optical active forms, enantiomers, diastereomers of compounds according to formula I, as well as their racemates and also pharmaceutically acceptable salts as well as the pharmaceutically active derivatives of the sulfonamide derivatives of formula I.

Preferred Ar^1 and Ar^2 in formula I are those that are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, aminoacyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halo, hydroxy, nitro, sulfonyl, sulfoxy, acetoxy, C_1-C_6- thioalkoxy. The most preferred Ar^1 is the 4-chlorophenyl, whereas the most preferred Ar^2 is the thienyl group.

In particularly preferred sulfonamide derivatives according to formula I, Ar^1 is a 4-chlorophenyl residue, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



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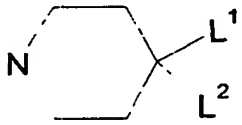


wherein,

L^1 and L^2 are independently selected from the group comprising or consisting of H, C_1-C_6-alkyl, e.g. a methyl group, cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and which is optionally fused with an aryl or a heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of aryl, heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-NHR^3, -NHR^3.

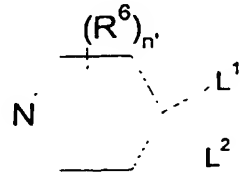
Therein, the residue R^3 is a substituent selected from the group comprising or consisting of H, C_1-C_6-alkyl, aryl, heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl.

All of the above mentioned aryl or heteroaryl groups could optionally be substituted by at least one of the groups selected from C_1-C_6-alkyl, like trihalomethyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, aminoacyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, C_1-C_6-thioalkoxy.

Also L^1 and L^2 taken together could form a 4-8-membered, substituted or unsubstituted, saturated cyclic alkyl or heteroalkyl group, like optionally substituted triazoles, tetra-

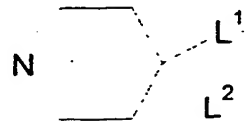
zoles. In a preferred embodiment L^1 and L^2 form together 5-6-membered saturated cyclic alkyl ring containing 2-3 nitrogen atoms, most preferably a triazole ring.

A particularly preferred embodiment of the present invention is related to the sulfonamide derivatives, wherein Y is a substituted or unsubstituted piperidine residue,



whereby R^6, n', L^1 and L^2 are as above defined.

In a particularly preferred embodiment of the sulfonamide derivatives according to formula I, Ar^1 is 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



whereby L^1 is H and L^2 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring, being preferably fused with a substituted or unsubstituted aryl group, e.g. a benzotriazole; or L^2 is -C(O)-R^3, or -NHR^3.

Thereby, R^3 is a substituent selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl.

Said aryl or heteroaryl groups may optionally be substituted by halogen, hydroxy, nitro, sulfonyl, e.g. a trifluoromethylsulfonyl group.

Specific examples of compounds of fomula I include the following :

4-Chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide
4-Chloro-*N*-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide
4-Chloro-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

3-Methoxy-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-[5-(4-pyrimidin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(1-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-pyridin-4-ylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-thiophen-2-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,5-dimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-cyclohexylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-[5-(4-phenethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-fluoro-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-cyano-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(chloro-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-piperidin-1-yl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-chloro-2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(6-methyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-hydroxy-4-phenyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(1-phenyl-methanoyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-[5-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-(5-{4-[(methyl-phenyl-carbamoyl)-methyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-{5-[4-(1-hydroxy-1,1-diphenyl-methyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(3'-Cyano-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(5-Nitro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(Chloro-trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(5-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzotriazol-1-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-(5-{4-[1-(4-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

5-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-5-cyano-6-methyl-nicotinic acid ethyl ester

4-Chloro-N-{5-[4-(cyano-bis-dimethylamino-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(methyl-trifluoromethyl-quinolin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazine-1-carboxylic acid tert-butyl ester

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

4-Chloro-N-{5-[4-(1-2,3-Dihydro-benzo[1,4]dioxin-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-((E)-3-Phenyl-allyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-phenyl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,4,5-trimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-tert-Butyl-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(5-cyano-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

{1-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperidin-4-yl}-carbamide acid tert-butyl ester

4-Chloro-N-[5-(4-phenyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(4-naphthalen-1-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(3,4-dichloro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-o-tolyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-((1R,4R)-5-Benzyl-2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(4-Benzyloxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-{5-[4-(2-Chloro-dibenzo[*b, f*][1,4]oxazepin-11-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

N-(4-Chloro-phenyl)-2-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-yl}-acetamide

4-Chloro-N-[5-(4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-Acetyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,5-dichloro-pyridin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-*tert* butyl-1*H*-indol-5-ylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(2-phenyl-ethanoylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-tetrahydro-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(6-chloro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-[5-(4-Benzotriazol-2-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-*N*-{5-[4-(5-chloro-benzotriazol-2-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-phenyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(4-trifluoromethyl-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-*p*-tolyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(4-dimethylamino-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2,6-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(3-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-naphthalen-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-naphthalen-1-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(2-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-pyridin-3-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-Benzo[1,2,5]oxadiazol-5-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2,4,6-trifluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-((E)-3-phenyl-allanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(2,6-dichloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(3,5-dimethoxy-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

Thereby, the most preferred compounds are those which are selected from the group consisting of :

4-Chloro-N-[5-(4-Benzotriazol-1-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-Benzo[1,2,5]oxadiazol-5-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide.

A further aspect of the present invention consists in the use of the sulfonamide derivatives according to formula I for the preparation of pharmaceutical compositions for the modulation of the JNK pathway associated disorders, in particular against neuronal disorders and/or against disorders of the immune system as well as said pharmaceutical compositions themselves. Preferred JNK pathways are the JNK2 and/or JNK3.

As above pointed out, the compounds of formula I are suitable to be used as a medicament. Some few of the compounds falling into the above generic formula I have been disclosed prior to the filing of the present application, whereby for 9 of them no medical or biological activity whatsoever was described so far. Hence, it is herein reported that both the novel and the few known compounds falling under the above set out generic formula I are indeed suitable for use in treating a whole variety of diseases, like disorders of the autoimmune system and neuronal system of mammals, notably of human beings. More specifically, the compounds according to formula I, alone or in the form of a pharmaceutical composition, are useful for the modulation of the JNK pathway,

more specifically for treatment or prevention of disorders associated with abnormal expression or activity of JNK, notably of JNK2 and 3. Said modulation usually preferably involves the inhibition of the JNK pathways, notably of the JNK2 and/or 3. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents.

Specifically, the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK2 or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arteriosclerosis, myocordial infarction, myocordial reperfusion injury.

Quite surprisingly it turned out that the inventively found compounds according to formula I do show a considerable activity as inhibitors of JNK2 and 3. According to a preferred embodiment, the compounds according to the invention are essentially inactive in view of 2 further apoptosis modulating enzymes, i.e. p38 and/or ERK2, belonging incidentally to the same family as JNK2 and 3. Hence, the compounds according to the present invention offer the possibility to selectively modulate the JNK pathway, and in particular to come to grips with disorders related to the JNK pathways, while being essentially inefficient with regard to other targets like said p38 and ERK2, so that they could indeed be viewed as selective inhibitors. This is of considerable significance, as these related enzymes are generally involved in different disorders, so that for the treatment of a distinct disorder, it is desired to employ a correspondingly selective medicament.

As a matter of fact, prior to the herein reported, surprisingly found pharmaceutically active sulfonamide derivatives according to formula I, nothing was known in respect of the use of small molecule chemical compounds as inhibitors of the JNK kinase pathway.

Still a further aspect of the present invention consists in the actually novel sulfonamide derivatives of formula I, i.e. those sulfonamide derivatives according to formula I that have not been disclosed by the prior art. Thereby, a total of 9 compounds have been disclosed by the CEREP company (www.cerep.fr) in as far as they are mentioned in a company catalogue, without any medical indication, though.

Generally, the compounds according to formula I of the CEREP company are only those wherein Ar^1 is 4-chlorophenyl and X is O and R^1 is H, Ar^2 is a thienyl group, while Y is a piperazino-, a 3-methyl piperazino-, a piperazino-3, 5-dione- or a piperidino group being substituted in the following way :

- where Y is a piperazino group, L^1 is diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl group, 4-chlorophenyl methyl,
- where Y is a 3-methyl piperazino, L^1 is 4-chlorophenyl methyl,
- where Y is a piperazino-3, 5-dione group, L^1 is 2-phenyl ethyl, and
- where Y is a piperidino group, L^1 is H, and L^2 is 2-hydroxy ethyl.

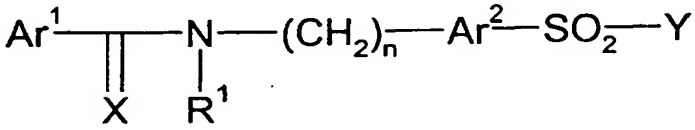
Compounds according to formula I that have been disclosed by the prior art together with a medical indication are those, wherein :

- Y is a piperidino- or a pyrrolidino group being substituted at the β–position of said sulfonamide nitrogen by one R^6 = benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, whereby Ar^1 is phenyl, Ar^2 is thienyl, X is oxygen, R^1 is hydrogen; L^1 and L^2 are H and n is 1 for the treatment of proliferative diseases (WO 96/30017).
- X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazino group, whereby L^1 is a substituent that includes a phenyl being imperatively substituted by a group –C(=NH)-NH_2 (benzamidine) or a protected form thereof to be used as factor XA inhibitors (WO 99/16751).

- Two further compounds are rather incidentally disclosed in WO 97/45403 (i.e. 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine as selective dopamine D3 ligand) and in WO 97/30992 (i.e. N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride to be used for inhibiting farnesyl-protein transferase).

- Finally, compounds of formula I wherein X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, said Y being imperatively substituted by an amido group (C=O)N(R,R') at the alpha position of the sulfonamide nitrogen are disclosed within WO 98/ 53814. Said compounds are mentioned to be useful in the inhibition of cell adhesion.

Hence, the entirely novel sulfonamide derivatives are those of the below set out general formula I whereby the above identified known compounds are excluded.



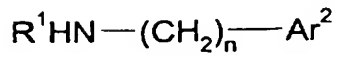
I

Still a further object of the present invention is a process for preparing the novel sulfamide derivatives according to formula I which have been set out above.

The sulfonamide derivatives of this invention can be prepared from readily available starting materials using the following general methods and procedures.

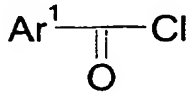
It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimisation procedures.

In a preferred method of synthesis, the sulfonamide derivatives of the invention are prepared by first coupling an amine of formula II:



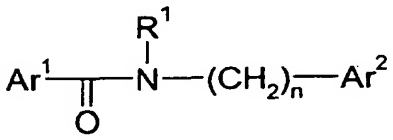
II

where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



III

where Ar^1 is as defined above, to provide an amide of formula IV:



IV

Amines of formula II are either known compounds or can be prepared from known compounds by conventional procedures. Preferred amines as starting materials include thien-2-yl-methylamine, furan-2-yl-methylamine, pyridyl-2-ylmethylamine and the like.

The acyl chlorides of formula III are also commercially available or previously described compounds. Preferred acyl chlorides include 4-chlorobenzoyl chloride, 4-fluorobenzoyl chloride, 4-trifluoromethylbenzoyl chloride and the like. If not known, the acid halide can be prepared by reacting the corresponding carboxylic acid with an inorganic acid halide, such as thionyl chloride, phosphorus trichloride or oxalyl chloride under conventional conditions.

Generally, this reaction is conducted upon using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either in pure form or in an inert solvent, such as carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, as *N,N*-dimethylformamide, may also be used in this reaction.

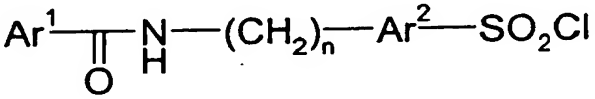
When an acyl halide is employed in the coupling reaction, it is typically reacted with amine II in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, an excess of amine II may be used to scavenge the acid generated during the reaction.

Alternatively, the carboxylic acid of compound III can be employed in the coupling reaction. The carboxylic acid of III are usually commercially available reagents or can be prepared by conventional procedures.

The coupling reaction of carboxylic acid of III (i.e. the acyl chloride) is conducted upon using any conventional coupling reagent including, for example, carbodiimides such as dicyclohexylcarbodiimide, N-(3-Dimethylaminopropyl)-N'-Ethylcarbodiimide and other promoting agents, such as *N,N*-carbonyl-diimidazole or PyBOP. This reaction can be conducted with or without the use of well known additives such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. which are known to facilitate the coupling of carboxylic acids and amines.

The coupling reaction using either acid halide III or its carboxylic acid is preferably conducted at a temperature of from about 0°C to about 6°C for about 1 to about 24 hours. Typically, the reaction is conducted in an inert aprotic polar solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like using about 1 to about 5 molar equivalents of the amine based on the carboxylic acid or its acid halide. Upon completion of the reaction, the carboxamide IV is recovered by conventional methods including precipitation, chromatography, filtration, distillation and the like.

The sulfonyl chorides of formula V necessary for the preparation of the sulfonyl-piperidines or piperazines of formula I are either commercially available or prepared using conventional sulfonating methods:



V

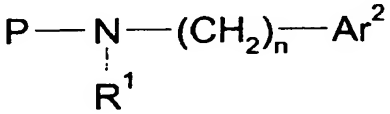
Preferred sulfonating reagent for use in this reaction is chlorosulfonic acid. Typically, the sulfonation reaction is conducted by treating the carboxamide of formula (IV) with about 5 to about 10 molar equivalent of the sulfonating reagent in an inert solvent, such as dichloromethane, at a temperature ranging from about –70°C to about 50°C. Preferably, the addition of chlorosulfonic acid takes place at –70°C and leads to the formation

of the intermediate sulfonic acid. Increasing the temperature to 20°C allows the formation of the sulfonyl chloride of formula V.

According to a further preferred method of preparation notably in case that the above pointed out method leading to the preliminary synthesis of sulfonyl chloride of formula V is not applicable, the sulfonyl piperidines and piperazines of this invention are prepared by the following steps:

- Protection of the amine function of compounds of formula II;
- Chlorosulfonylation of the aromatic group;
- Formation of the sulfonamide function;
- Deprotection of the protectiong group;
- Acylation of the above generated free amine;

Amines of formula II are protected with a suitable protecting group of an amine moiety to provide intermediate of formula VI wherein P denotes the protecting group.

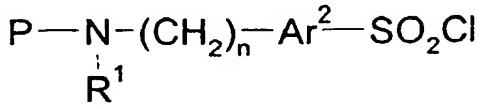


VI

Numerous protecting groups P of the amine function as well as their introduction and removal, are well described in T.W. Greene and G.M. Wuts, Protecting groups in Organic Synthesis, Third Edition, Wiley, New York, 1998, and references cited therein. Preferred are protecting groups that are acids and bases stable and can be further removed by using metal transition complexes such as palladium complexes, for example the allylcarbamate group (Alloc) or the N,N'-bisallyl group. Another preferred protecting group is the maleimide group which is stable in a all range of experimental conditions.

The introduction of said groups can be performed by reacting the corresponding bisallylcarbonate anhydride or allylbromide or maleic anhydride in the presence of a base such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like in a aprotic

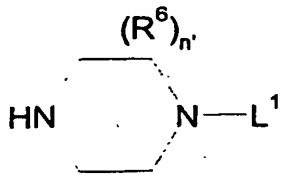
solvent such as N,N-dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like at a temperature ranging from about 0°C to about 80°C. Compounds of formula VI are then sulfonated using a conventional very mild sulfonating procedure that allows the obtention of sulfonyl chloride of formula VII.



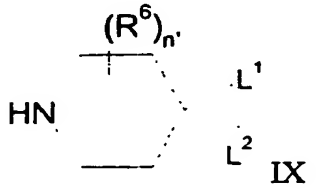
VII

Typically, protected amine VI is treated with a base such as n-butyllithium or tert-butyllithium under an inert atmosphere, in a polar aprotic solvent such as tetrahydrofuran, ether or dioxanne at a temperature ranging from –70°C to 0°C during a time ranging from 15 minutes to 4 hours. The so formed anion is then treated with SO_2Cl_2 or most preferably SO_2 by bubbling the gas into the reaction mixture at a temperature ranging from –70°C to 20°C during a time ranging from 5 minutes to 1 hour. The sulfonate obtained is then transformed "in situ" to the sulfonyl chloride of formula VII by contacting with *N*-chlorosuccinimide at a temperature ranging from 0°C to 70°C.

The sulfonamide derivatives of formula I are then prepared from the corresponding above mentioned sulfonyl chloride V or VII, by reaction either with a piperazine or piperidine derivative of the general formula VIII or IX.



VIII or



IX

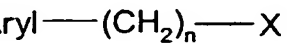
whereby L^1 and L^2 are as above defined.

The amines of formula VIII or IX are either commercially available compounds or compounds that can be prepared by known procedures.

Typically, piperazines of type VIII can be prepared upon using conventional methods known by a person skilled in the art.

For L^1 and/or L^2 = aryl, suitable methods of preparation are described in *Tetrahedron Lett.* **1996**, *37*, 8487-8488 and references cited therein.

For L^1 and/or L^2 = aryl C_1-C_6 alkyl, a further preferred method is the reaction of the corresponding piperazine or mono-*N*-protected piperazine with compounds of formula X

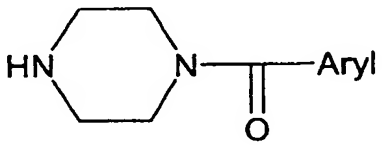


X

wherein X is Cl, Br, I, OTs, OMs

The reaction is generally conducted in the presence of a base such as triethylamine, diisopropylethylamine, potassium carbonate and the like in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

For L^1 and/or L^2 = -C(S)-, a further preferred method is the conversion of compounds of type XI using the Lawesson's reagent which allows the transformation of an amide into a thioamide group as described in *Bull. Soc.Chim. Belgium*, **1978**, *87*, 229.



XI

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chlorides V with an amine of formula VIII in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

Alternatively, the sulfonamide derivatives of formuly I are readily prepared from the corresponding sulfonyl chloride V or VII, by reaction with a piperidine of general formula IX

Piperidines of formula IX are either commercially available compounds or compounds that can be prepared by known procedures.

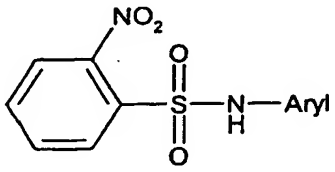
Typically, piperidines of type IX can be prepared using conventional methods known by one skilled in the art and described by way of examples in *J. Pharm. Sci.* **1972**, *61*, 1316; *J. Heterocyclic. Chem.*, **1986**, *23*, 73; *Tetrahedron Lett.*, **1996**, *37*, 1297, US 5106983, WO/9113872 and WO/9606609.

Preferred methods of obtention of piperidines of formula IX are the following:

For L^1 = H and L^2 = (CH_2)n-Aryl wherein n = 0,1,2; addition of an organometallic species such as $Ar^3(CH_2)_nLi$ or $Ar^3(CH_2)_nMgBr$ on mono-protected 4-piperidone followed by reduction of the so-formed double bound which allows the formation of compounds of type IX.

For L^2 = -NR-(CH_2)n-Aryl wherein n = 0,1,2, a preferred method is the reductive amination of 4-piperidone with amines of type Aryl-(CH_2)n-NR-H.

A further preferred method in the case where n = 0 is a "Mitsunobu type" coupling between an activated aniline of type XII with mono-N-protected 4-piperidol as described in *Tetrahedron Lett.* **1995**, *36*, 6373-6374.

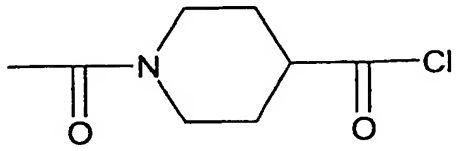


XII

Deprotection of the sulfamino group is then carried out using thiophenol in the presence of potassium carbonate.

For L^2 = -NR^3'C(O)R^3, -NR^3'C(O)NR^3'R^3, NR^3'SO_2-R^3, a preferred method of synthesis of compounds of formula IX is the reaction of commercially available N-BOC-4-aminopiperidine with respectively acyl chlorides, isocyanates and sulfonyl chloride under classical conditions very well known by one skilled in the art.

When L^2 = -CO-Aryl, compounds of formula IX are readily prepared by contacting well chosen aromatic or heteroaromatic rings with intermediate of type XIII

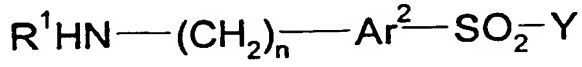


XIII

in the presence of a Lewis acid such as aluminum trichloride or titanium tetrachloride in a polar aprotic solvent such as dichloromethane. Intermediate XIII can be easily obtained by first acetylation of piperid-4-yl carboxylic acid and their formation of the acyl chloride by treatment with thionyl chloride.

The sulfonamides of formula I are readily prepared by contacting the sulfonyl chloride V with an amine of formula IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C.

The sulfonamides of formula XIV are readily prepared by contacting the sulfonyl chloride VII with an amine of formula VIII or IX in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of examples, triethylamine, diisopropylethylamine, N-methylmorpholine and the like. The reaction is preferably conducted in solvent such as N,N-dimethyformamide, dimethylsulfoxide, N-methylpyrrolidone, ethanol, acetonitrile at a temperature from about 0° to about 100°C. The use of sulfonyl chloride of type VII leads to amines that have to be deprotected using well known methods by one skilled in the art to afford amine of general formula XIV

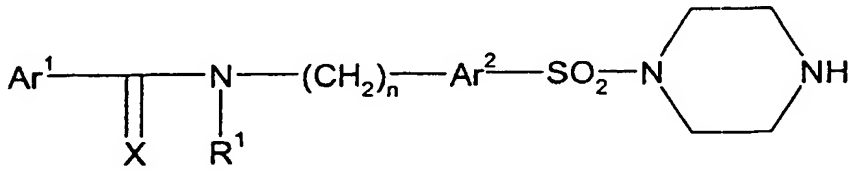


XIV

wherein R^1, Ar^2, Y and n are as above defined.

Derivatives of type XIV are then acylated according to described methods for the preparation of amides by condensation of amines with acid chlorides or carboxylic acids in the prefered conditions described above leading to compounds of general formula I

In the particular case of compounds of general formula I where Y represents a piperazine derivative, an alternative method of preparation which has also to be considered as part of this invention, said method of preparation consisting in the condensation of a piperazine derivative of formula XV



XV

with electrophiles L^1 which will be chosen depending on the nature of L^1 (see the above definition of L^1, L^2). Procedures and methods to perform these types of condensation are well-known and have been well described on various synthesis of N-substituted piperazine derivatives.

If the above set out general synthetic methods are not applicable for the obtention of compounds of formula I, suitable methods of preparation known by a person skilled in the art should be used. For example, when Ar^2 is phenyl, one should start from commercially available 4-cyanophenyl sulfonyl chloride and applies conventional methods known by a person skilled in the art to reach sulfonamide derivatives of formula I.

A final aspect of the present invention is related to the use of the compounds according to formula I for the modulation of the JNK pathway, the use of said compounds for the preparation of pharmaceutical compositions for the modulation of the JNK pathway as well as the formulations containing the active compounds according to formula I. Said modulation of the JNK pathway is viewed as a suitable approach of treatment for various disorders. When employed as pharmaceuticals, the sulfonamide derivatives of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the

scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides the compounds of formula I for use as JNK inhibitor, notably JNK2 and JNK3, for the treatment of disorders of the immune as well as the neuronal system of mammals, notably of humans, either alone or in combination with other medicaments.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, the sulfonamides derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders.

More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the sulfonamide compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the sulfonamide compound of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein be reference.

The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained

release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention.

Examples

Example 1: Preparation of 4-chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-yl-methyl]-benzamide **1**

4-Chloro-*N*-thiophen-2-ylmethyl-benzamide **1a**

A solution of 4-chlorobenzoyl chloride (0.114 mol) in 50 ml dry CH_2Cl_2 was added over 30 min to a stirred solution of 2-aminomethyl-thiophene (0.137 mol) and $^iPr_2NEt$ (0.25 mol) in CH_2Cl_2 (200ml) at 0 °C. A white solid was formed and the reaction was allowed to warm to room temperature over 1 h. The mixture was diluted with 200 ml of CH_2Cl_2, washed twice with HCl aq. (0.1N) and dried over $MgSO_4$. Evaporation of the solvents afforded 28 g (98%) of the title benzamide as a white solid: mp 153-54°C, ^1H NMR ($CDCl_3$) δ 7.9 (d, J = 8.67 Hz, 2H), 7.58 (d, J = 8.67 Hz, 2H), 7.44 (dd, J = 3.77, 1.13 Hz, 1H), 7.22 (d, J = 5.27 Hz, 1H), 7.16 (dd, J = 3.39, 5.27 Hz, 1H), 6.62 (br d, 1H), 4.98 (d, J = 5.65 Hz, 2H).

5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl chloride **1b**

Chlorosulfonic acid (20.1 ml, 198 mmol) in CH_2Cl_2 (80 ml) was added dropwise to a solution of **1a** (10 g, 40 mmol) in CH_2Cl_2 (500 ml) at –80°C. The mixture was allowed to reach room temperature in 5h.. The reaction mixture was poured on ice and quickly extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to dryness which afforded 8.8 g (63%) of desired sulfonyl chloride **1b**; mp 133-35°C, ^1H NMR (DMSO-*d6*) δ 9.21 (t, J = 6.4 Hz, 1H), 7.87 (d, J = 8.67 Hz, 2H), 7.53 (d, J = 8.67 Hz, 2H), 6.91 (d, J = 3.39 Hz, 1H), 6.77 (d, J = 3.39 Hz, 1H), 4.53 (d, J = 3.77 Hz, 2H).

4-Chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **1**

A solution of **1b** (1 g, 2.9 mmol) in 0.5 ml DMF and 2 ml CH_2Cl_2 was added slowly at 0°C to piperazine (985 mg, 11.4 mmol) in CH_2Cl_2 (11 ml). The reaction was stirred for 2h while room temperature was reached. The reaction mixture was washed with sat. $NaHCO_3$ and dried over $MgSO_4$. After evaporating the solvent 1.76 g (62%) of **1c** was isolated. ^1H NMR (DMSO-*d6*) δ 9.38 (t, J = 5.27 Hz, 1H), 7.90 (d, J = 8.67 Hz, 2H), 7.56 (d, J = 8.67 Hz, 2H), 7.46 (d, J = 3.77 Hz, 1H), 7.18 (d, J = 4.14 Hz, 1H), 4.67 (d, J = 6.03 Hz, 2H), 2.66-2.84 (m, 8H),

Example 2 : Preparation of 4-chloro-*N*-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **2**

To a stirred solution of 1-pyridin-2-yl-piperazine (53 mg, 0.32 mmol) and iPr_2NEt (110 µl, 0.64 mmol) in CH_2CL_2(5ml) was added **1b** (100 mg, 0.29 mmol) in DMF (2 ml). After 1 h the reaction mixture was washed with HCl (0.1 N) and sat. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated and residue was filtered through silica gel using CH_2Cl_2/MeOH 2% as eluant. **2** was isolated as white solid (99 mg, 72%). ^1H NMR (DMSO-*d6*) δ 9.34 (t, J = 5.65 Hz, 1H), 8.07 (dd, J = 3.39, 1.51 Hz, 1H), 7.88 (d, J = 8.67 Hz, 2H), 7.48-7.53 (m, 3H), 7.50 (d, J = 3.77 Hz, 1H), 7.18 (d, J = 3.77 Hz, 1H), 6.81 (d, J = 8.67 Hz, 2H), 6.66 (d, J = 5.27 Hz, 1H), 6.64 (d, J = 4.16 Hz, 1H), 4.65 (d, J = 6.03 Hz, 2H), 3.58-3.62 (m, 4H), 2.96-3.00 (m, 4H).

Example 3 : Preparation of 4-chloro-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **3**

To a stirred solution of **1** (36 mg, 0.09 mmol) and iPr_2NEt (32 µl, 0.189 mmol) in $CHCl_3$ (2ml) was added 4-fluoro-benzoyl chloride (44 mg, 0.08 mmol). After 4 h the reaction mixture was washed with HCl (0.1 N) and sat. NaCl solution, and dried over $MgSO_4$. The solvent was evaporated and residue was filtered through silica gel using AcOEt/MeOH 1% as eluant to afford **3** as white solid (44 mg, 94%).

Example 4: Preparation of 3-Methoxy-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **4**

Diallyl-thiophen-2-ylmethylamine **4a**

Allyl bromide (55 ml, 65.4 mmol) was added to a solution of 2-aminomethyl-thiophene (24 ml, 23.3 mmol) and *i*-Pr_2NEt (120 ml, 70.1 mmol) in CH_2Cl_2 (270 ml). The moderately exothermic reaction spontaneously reached the reflux temperature after 1 h. The reaction was cooled by means of an ice bath and stirred for 14 h at r.t. whereupon an undesired precipitate appeared. This precipitate (45 g) was removed by filtration. The organic layer was evaporated and diluted with EtOAc, whereupon more precipitate appeared (45 g), which was removed by filtration. The EtOAc solution was filtered over SiO_2 and concentrated to give 36.1 g (80%) of the title diallylamine as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.25 (br. d, J = 5.9 Hz, 1H), 6.98 (br. dd, J = 5.1, 2.8 Hz, 1H), 6.94–6.92 (m, 1H), 5.99–5.86 (m, 2H), 5.29–5.18 (m, 4H), 3.85 (s, 2H), 3.16 (dd, J = 6.3, 0.9 Hz, 4H).

5-Diallylaminomethyl-thiophene-2-sulfonyl chloride **4b**

A solution of the allyl-protected thiophene **4a** (6.2 g, 32.1 mmol) in Et_2O was cooled to – 70°C by means of an acetone/dry ice bath. A solution of *t*-BuLi in pentane (21.38 ml, 1.5M, 32.1 mmol) was added over 2 min whereupon the internal temperature momentarily rose to –50°C and the mixture turned orange. After 10 min., SO_2 was bubbled for 2 min, which led to the immediate formation of a thick precipitate. The reaction was allowed to reach 0°C, and a suspension of NCS (4.63 g, 32.1 mmol) in THF (20 ml) was added, whereupon the slurry turned purple. After 45 min at r.t., the mixture was filtered over SiO_2, eluting with EtOAc. Evaporation, dilution with EtOAc:hexane 1:5 and filtration over SiO_2 gave 5.0 g (53%) of the title sulfonyl chloride **4b** as a pale brown oil which was used without further purification.

1-[4-(5-Diallylaminomethyl-thiophene-2-sulfonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-methanone **4c**

Preparation of **4c** is performed as described above by first adding piperazine to **4b** (Example 1) and second acylation with 4-flurophenyl benzoyl chloride (Example 3).

1-[4-(5-Aminomethyl-thiophene-2-sulfonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-methanone **4d**

A solution of the bisallylamine **4c** (7.25 mmol), N,N'-dimethylbarbituric acid (NDMBA 18.1 mmol), and $Pd(PPh_3)_4$ (148.8 mg, 0.13 mmol) in CH_2Cl_2 was de-gassed by bubbling argon for 10 min. The reaction was stirred for 3 h at r.t. whereupon the desired amine **4d** precipitated as its NDMBA salt. The mixture was diluted with EtOAc (200 ml) and hexane (200 ml) and washed with water (3 x 50 ml). The crude compound **4d** was pure enough to be used in the next step without further purification.

3-Methoxy-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide 4

Acylation of intermediate **4d** was carried out using 3-methoxyphenyl benzoyl chloride in the conditions described above (Example 3)

Upon using the procedures described in the above examples1-4 and the appropriate starting material and reagents, the following additional sulfonamides derivatives of formula I could be obtained:

4-Chloro-N-[5-(4-pyrimidin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **5**

4-Chloro-N-{5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **6**

4-Chloro-N-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **7**

4-Chloro-N-{5-[4-(2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **8**

4-Chloro-N-{5-[4-(4-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **9**

4-Chloro-N-[5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide **10**

4-Chloro-N-{5-[4-(1-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **11**

4-Chloro-N-{5-[4-(4-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **12**

4-Chloro-N-{5-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **13**

4-Chloro-N-{5-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **14**

4-Chloro-N-[5-(4-pyridin-4-ylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **15**

4-Chloro-N-{5-[4-(2-thiophen-2-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **16**

4-Chloro-N-{5-[4-(3,5-dimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **17**

4-Chloro-N-[5-(4-cyclohexylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **18**

4-Chloro-N-{5-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **19**

4-Chloro-N-[5-(4-Benzyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide **20**

4-Chloro-N-[5-(4-phenethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **21**

4-Chloro-N-{5-[4-(4-fluoro-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **22**

4-Chloro-N-{5-[4-(2-cyano-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **23**

4-Chloro-N-{5-[4-(chloro-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **24**

4-Chloro-N-{5-[4-(3-piperidin-1-yl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **25**

4-Chloro-N-{5-[4-(4-chloro-2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **26**

4-Chloro-N-{5-[4-(6-methyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **27**

4-Chloro-N-[5-(4-hydroxy-4-phenyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **28**

4-Chloro-N-{5-[4-(1-phenyl-methanoyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **29**

4-Chloro-N-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **30**

4-Chloro-N-[5-(4-Benzyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide **31**

4-Chloro-N-[5-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl)-thiophen-2-ylmethyl]-benzamide **32**

4-Chloro-N-(5-{4-[(methyl-phenyl-carbamoyl)-methyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **33**

4-Chloro-N-{5-[4-(1-hydroxy-1,1-diphenyl-methyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **34**

4-Chloro-N-[5-(3'-Cyano-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide **35**

4-Chloro-N-{5-[4-(5-Nitro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **36**

4-Chloro-N-{5-[4-(Chloro-trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **37**

4-Chloro-N-{5-[4-(5-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **38**

4-Chloro-N-{5-[4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **39**

4-Chloro-N-[5-(4-Benzotriazol-1-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **40**

4-Chloro-N-(5-{4-[1-(4-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **41**

4-Chloro-N-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **42**

5-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester **43**

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-5-cyano-6-methyl-nicotinic acid ethyl ester **44**

4-Chloro-N-{5-[4-(cyano-bis-dimethylamino-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **45**

4-Chloro-N-{5-[4-(methyl-trifluoromethyl-quinolin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **46**

4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazine-1-carboxylic acid tert-butyl ester **47**

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid **48**

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid **49**

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid **50**

4-Chloro-N-{5-[4-(1-2,3-Dihydro-benzo[1,4]dioxin-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **51**

4-Chloro-N-{5-[4-((E)-3-Phenyl-allyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **52**

4-Chloro-N-{5-[4-(3-phenyl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **53**

4-Chloro-N-{5-[4-(3,4,5-trimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **54**

4-Chloro-N-{5-[4-(4-tert-Butyl-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **55**

4-Chloro-N-{5-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **56**

4-Chloro-N-{5-[4-(2-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **57**

4-Chloro-N-{5-[4-(4-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **58**

4-Chloro-N-{5-[4-(5-cyano-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **59**

{1-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperidin-4-yl}-carbamide acid tert-butyl ester **60**

4-Chloro-N-[5-(4-phenyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **61**

4-Chloro-N-[5-(piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **62**

4-Chloro-N-[5-(4-naphthalen-1-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **63**

4-Chloro-N-{5-[4-(3,4-dichloro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **64**

4-Chloro-N-{5-[4-(3-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **65**

4-Chloro-N-{5-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **66**

4-Chloro-N-[5-(4-o-tolyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **67**

4-Chloro-N-[5-((1R,4R)-5-Benzyl-2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-thiophen-2-ylmethyl]-benzamide **68**

4-Chloro-N-[5-(4-Benzyloxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide **69**

4-Chloro-N-{5-[4-(2-Chloro-dibenzo[*b, f*][1,4]oxazepin-11-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **70**

N-(4-Chloro-phenyl)-2-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-yl}-acetamide **71**

4-Chloro-N-[5-(4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **72**

4-Chloro-N-{5-[4-(4-Acetyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **73**

4-Chloro-N-{5-[4-(3,5-dichloro-pyridin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **74**

4-Chloro-N-{5-[4-(3-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **75**

4-Chloro-N-[5-(4-Benzyl-4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **76**

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **77**

4-Chloro-N-{5-[4-(2-*tert* butyl-1*H*-indol-5-ylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **78**

4-Chloro-*N*-{5-[4-(2-phenyl-ethanoylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **79**

4-Chloro-*N*-{5-[4-(1-tetrahydro-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **80**

4-Chloro-*N*-{5-[4-(6-chloro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **81**

4-Chloro-*N*-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **82**

4-Chloro-*N*-[5-(4-Benzotriazol-2-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide **83**

4-Chloro-*N*-{5-[4-(5-chloro-benzotriazol-2-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **84**

4-Chloro-*N*-{5-[4-(1-phenyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **85**

4-Chloro-N-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **86**

4-Chloro-*N*-(5-{4-[1-(4-trifluoromethyl-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **87**

4-Chloro-*N*-{5-[4-(1-*p*-tolyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **88**

4-Chloro-*N*-(5-{4-[1-(4-dimethylamino-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **89**

4-Chloro-*N*-(5-{4-[1-(2-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **90**

4-Chloro-*N*-(5-{4-[1-(2,6-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **91**

4-Chloro-*N*-(5-{4-[1-(3-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **92**

4-Chloro-*N*-{5-[4-(1-naphthalen-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **93**

4-Chloro-*N*-{5-[4-(1-naphthalen-1-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **94**

4-Chloro-*N*-(5-{4-[1-(2-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **95**

4-Chloro-*N*-{5-[4-(1-pyridin-3-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **96**

4-Chloro-*N*-{5-[4-(1-Benzo[1,2,5]oxadiazol-5-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **97**

4-Chloro-*N*-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **98**

4-Chloro-*N*-(5-{4-[1-(2,4,6-trifluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **99**

4-Chloro-*N*-{5-[4-((E)-3-phenyl-allanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide **100**

4-Chloro-*N*-(5-{4-[1-(2,6-dichloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **101**

4-Chloro-*N*-(5-{4-[1-(3,5-dimethoxy-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide **102**

The following tables provides HPLC data and mass spectroscopy data of the above mentioned examples. [1],[2].

Compounds	HPLC rt. (min)	purity (%)	HPLC gradient	Mass M+1	M-1
5	7.95	98	a	478	476
6	15.82	93	b	545	543
7	17.87	97	c	477	475
8	14.43	99	b	521	519
9	13.99	93.3	b	522	520
10	11.83	94	b	478	476
11	11.76	82	b	494	492
12	11.98	78	b	492	490
13	11.05	90	b	511	509
14	10.44	89	b	527	525
15	11.62	89	b	491	489
16	14.58	90	b	510	508
17	14.04	93	b	536	534
18	17.27	88	b	496	494
19	14.59	88	b	506	504
20	14.75	82	b	490	488
21	10.27	93	b	504	502
22	14.82	91	b	508	506
23	14.14	87	b	501	499
24	16.49	94	b	578.5	576.5
25	7.87	95	b	525	523
26	15.38	99	b	555.5	553.4
27	9.3	91	b	491	489
28	12.84	94	b	491	489
29	14.35	90	b	503	501
30	12.22	93	b	531	529
31	16.03	93	b	489	487
32	13.14	89	b	545	543

[1] HPLC conditions: column C18, 242 nm, Conditions: a- 50% buffer $KHPO_4$-50% MeCN, b- MeCN, 0.09%TFA, 0 to 100% (20min), c- MeCN, 0.09%TFA, 0 to 100% (30min).
[2] Mass spectrum APCI

33	9.86	97	b	547	545
34	15.36	96	b	581	579
35	13.06	86	b	503	501
36	13.76	76	b	522	520
37	16.32	90	b	579.5	577.6
38	14.88	80	b	545	543
39	14.63	95	b	545	543
40	13.06	98	b	516	514
41	12.75	96	b	549	547
42	14.72	95	b	539	537
43	16.13	93	b	659	657
44	14.97	89	b	588	586
45	12.79	85	b	588	586
46	15.88	96	b	609	607
47	14.04	94	b	500	498
48	12.9	73	b	617	615
49	13.05	87	b	634	632
50	13.1	96	b	633	631
51	13.5	95	b	562	560
52	10.65	93	b	516	514
53	10.61	97	b	518	516
54	13.16	90	b	566	564
55	11.81	95	b	546	544
56	14.93	90	b	494	492
57	12.1	93	b	492	490
58	14.42	91	b	545	543
59	13.15	94	b	502	500
60	13.77	98	b	514	512
61	14.18	94	b	476	474
62	13.13	96	b	399	397
63	16.38	75	b	526	524
64	16.48	81	b	545	543
65	15.86	93	b	544	542
66	14.79	95	b	559	557
67	15.64	79	b	490	488
68	9.51	97	b	502	500

69	15.08	93	b	505	503
70	12.86	94	b	627.5	625.6
71	12.76	84	b	531	529
72	10.35	95	b	415	413
73	13.15	96	b	518	516
74	13.89	92	b	546	544
75	14.24	89	b	506	504
76	13.72	92	b	505	503
77	15.53	96	b	622	620
78	11.55	97	b	585	583
79	12.61	88	b	532	530
80	10.87	94	b	498	496
81	14.93	95	b	511	509
82	15.49	91	b	510	508
83	6.56	91	a	516	514
84	7.12	98	a	550	548
85	12,25	85	b	504	502
86	12,53	96	b	540	538
87	13,82	98	b	572	570
88	12,98	94	b	518	516
89	10,55	93	b	547	545
90	12,42	98	b	522	520
91	12,61	96	b	540	538
92	12,62	93	b	522	520
93	13.6	90	b	554	552
94	13.44	93	b	554	552
95	12.26	87	b	549	547
96	9.17	84	b	505	503
97	12.75	99	b	546	544
98	12.84	90	b	540	538
99	13.06	89	b	558	556
100	6.18	93	d	530	528
101	13.19	95	b	574	572
102	12.78	99	b	564	562

Example 4 : Preparation of a pharmaceutical formulation

The following formulation examples illustrate representative pharmaceutical compositions according to the present invention being not restricted thereto.

Formulation 1 – Tablets

A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets (80-90 mg of active sulfonamide compound per tablet) in a tablet press.

Formulation 2 – Capsules

A sulfonamide compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active sulfonamide compound per capsule).

Formulation 3 – Liquid

A sulfonamide compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously prepared solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 – Tablets

A sulfonamide compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active furansulfonic acid compound) in a tablet press.

Formulation 5 – Injection

A sulfonamide compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

Example 5 : Biological assays

JNK3 in vitro assays: JNK3 and/or 2 assays are performed in 96 well MTT plates, by incubation of 0.5 µg of recombinant, pre-activated GST-JNK3 with 1 µg of recombinant, biotinylated GST-c-Jun and 2 µM $^{33}\gamma$-ATP (2 nCi/µl), in the presence or absence of sulfonamide inhibitors and in a reaction volume of 50 µl containing 50 mM Tris-HCl, pH 8.0; 10 mM $MgCl_2$; 1 mM Dithiothreitol, and 100 µM $NaVO_4$. The incubation is performed for 120 min. at R.T and stopped upon addition of 200 µl of a solution containing 250 µg of Streptavidine-coated SPA beads (Amersham, Inc.)*, 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP, in phosphate saline buffer. After incubation for 60 minutes at RT, beads are sedimented by centrifugation at 1500 x g for 5 minutes, resuspended in 200 µl of PBS containing 5 mM EDTA, 0.1% Triton X-100 and 50 µM ATP and the radioactivity measured in a scintillation β counter, following sedimentation of the beads as described above. By substituting GST-c Jun for biotinylated GST-$_1$ATF$_2$ or myelin basic protein, this assay can be used to measure inhibition of preactivated p38 and ERK MAP Kinases, respectively.

Sympathetic Neuron Culture and Survival Assay : Sympathetic neurons from superior cervical ganglia (SCG) of newborn rats (p4) are dissociated in dispase, plated at a density of 10^4 cells/cm^2 in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 µg/ml NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 10^5M. Cell death is induced at day 4 after plating by exposing the culture to medium containing 10 µg/ml of anti NGF antibody (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of sulfonamide inhibitors. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/ml of 3-(4,5-dimethylthiazol-2-yl)2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are resuspended in DMSO, transferred to a 96 MTT plate and cell viability is evaluated by measuring optical density at 590 nm.

Culture of THP-1 monocytes Assay:

THP-1 cells, a human monocyte cell line (American Type Culture Collection # TIB 202) were cultured in RPMI 1640 medium (Gibco, BRL) plus 10% fetal bovine serum in T-flasks. The cell suspension in the medium is diluted to give 2.10^6 cells/ml. The cells were plated (2.10^5 cells/well) on a 96-well plate containing different concentration of test compound (final concentration of compounds 30, 10, 3, 1, 0.3, 0.1 μM). This mixture was incubated 30 minutes at 37°C in a humidified CO_2 atmosphere. Cells were then treated with LPS (1 μg/ml final concentration) and incubate 4-5 hours at 37°C prior to performing ELISA test on the supernatant.

TNF-α ELISA Assay:

TNF-α secretion into the medium by LPS-stimulated THP-1 cells, in presence or absence of test compounds was assayed by ELISA. Briefly, a microtiter plate coated with a monoclonal anti-human TNF-α antibody (MAB610) (R & D Systems). Standards and samples were pipetted into the wells the immobilized antibody captured any TNF-α present. Unbound proteins were washed away and a biotinylated anti-human TNF-α antibody (BAF210) (R & D Systems) was added to the wells. After washing the unbound antibody away streptavidin-HRP (Zymed) was added. After washing the unbound streptavidin-HRP, substrate solution (citric acid/ Na_2HPO_4 (v/v), H_2O_2, OPD) was added, color development was stopped with H_2SO_4 20% and optical density was measured 450 nm with correction at 570 nm. The amount of TNF–α present in the samples were calculated based upon a standard curve. Assay was run in triplicate wells.

Biological Results

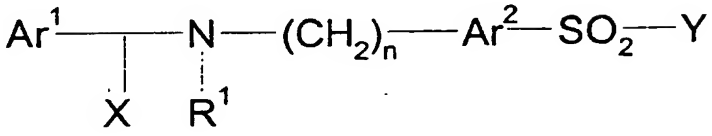
The activities of the sulfonamide derivatives claimed in the formula I were assessed using the above described *in vitro* and *in vivo* biologicals assays. Representative values are given in the table shown below:

AS#	*JNK3*	*JNK2*	*p38*	*ERK2*
5	3.0	2.2	>30	>30
40	0.15	0.22	>30	>30
42	0.61	0.58	>30	>30
77	0.30	0.33	>30	>30
97	0.53	0.72	>30	>30

The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC_{50} (μM), i.e. the amount necessary to achieve 50% inhibition of said target (e.g. JNK2). AS# denotes an exemplary test compound as set out with its number in the above examples. From the above table it could be derived that said test compounds according to formula I do have a significant effect both on JNK2 and 3, but virtually no effect onto p38 and ERK2, thus delivering a quite selective inhibitory effect.

Claims

1. Sulfonamide derivatives according to formula I



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with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups,
X is O or S, preferably O;
R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;
n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

with the proviso that if Ar^1 is 4-chlorophenyl, X is O, R^1 is H, Ar^2 is thienyl, while Y is a piperazino group, L^1 shall not be diphenylmethyl, benzo[1,3]dioxol-5-yl-methyl, 4-methoxy phenyl, 2-hydroxyethyl, methyl, 4-chlorophenyl methyl, and if Y is a 3-methyl piperazino, L^1 shall not be 4-chlorophenyl methyl, and if Y is piperazino-3, 5-dione, L^1 shall not be 2-phenyl ethyl,

with the further proviso that if Ar^1 is 4-chlorophenyl, X is O, R^1 is H, Ar^2 is thienyl, while Y is a piperidino group with L^1 being H, L^2 shall not be 2-hydroxy ethyl;

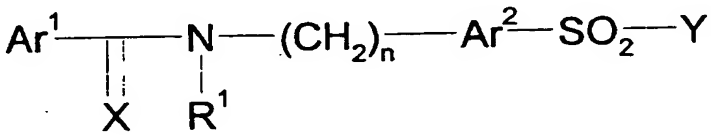
with the further proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β–position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, while Ar^2 is thienyl, X is oxygen, R^1 is hydrogen and n is 1, Ar^1 shall not be a phenyl group;

with the further proviso that if X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

2. Sulfonamide derivatives according to formula I



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with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups,

X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide, for use as a medicament;

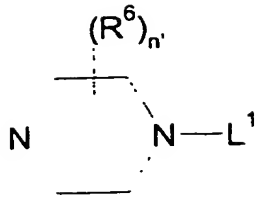
with the proviso that if Y is a piperidino- or a pyrrolidino group being substituted at the β–position of the piperidino- or a pyrrolidino nitrogen by a benzo[5, 6]cyclohepta[1, 2b]pyridine, or a benzo[5, 6]cyclohept (3,4) ene [1, 2b]pyridine, while Ar^2 is thienyl, X is oxygen, R^1 is hydrogen and n is 1, Ar^1 shall not be a phenyl group;

with the further proviso that if X is oxygen, R^1 is hydrogen and n is 1, while Y is a piperazine, said piperazine at the para-nitrogen nitrogen shall not be substituted by a group containing a benzamidine or a protected form thereof;

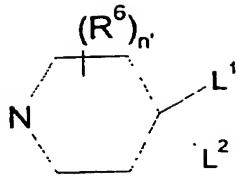
with the further proviso that the compounds 2-{[2-(benzoylaminomethyl)-thiophene]-5-sulfonyl}-1,2,3,5,6,7-hexahydro-N,N-dipropylcyanopent[f]isoindol-6-amine and N-[[5-[[7-cyano-1,2,3,5-tetrahydro-1-(1H-imidazol-4-yl-methyl)-3-(phenylmethyl)-4H-1,4-benzodiazepin-4-yl]sulfonyl]–2-thienyl] methyl] benzamide and its hydrochloride are excluded;

with the final proviso that if X is oxygen and Y is a 4-8 membered saturated cyclic alkyl containing one or two nitrogen atoms, Y shall not be substituted by a group (C=O)N(R,R') at the α-position of the sulfonamide nitrogen.

3. A sulfonamide derivative according to claim 1 or 2, wherein Y is selected from the group comprising or consisting of a piperazino- or piperidino group of the general formula



or



whereby, L^1 and $L^2$are independently selected from each other from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, substituted or unsubstituted cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with aryl or heteroaryl; or L^1 and L^2 are independently selected from the group comprising or consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl, -C(O)-OR^3, -C(O)-R^3, -C(O)-$NR^{3'}R^3$, -$NR^{3'}R^3$, -$NR^{3'}C(O)R^3$, -$NR^{3'}C(O)NR^{3'}R^3$, -(SO)R^3, -(SO_2)R^3, -NSO_2R^3, -$SO_2NR^{3'}R^3$,

with R^3, $R^{3'}$ being substituents independently selected from the group comprising or consisting of H, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl-C_1-C_6-alkyl, substituted or unsubstituted heteroaryl-C_1-C_6-alkyl;

said aryl or heteroaryl groups being optionally substituted C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, aminoacyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, sulfoxy, C_1-C_6-thioalkoxy,

or L^1 and L^2 taken together form a 4-8-membered, substituted or unsubstituted saturated cyclic alkyl or heteroalkyl group; and

R^6 is selected from the group comprising or consisting of hydrogen, substituted or unsubstituted C_1-C_6-alkyl, substituted or unsubstituted C_1-C_6-alkoxy, OH, halogen, nitro, cyano, sulfonyl, oxo (=O), and

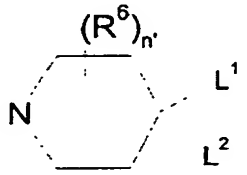
n' is an integer from 0 to 4, preferably 1 or 2.

4. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 and Ar^2 are independently selected from the group comprising or consisting of phenyl, thienyl, furyl, pyridyl, optionally substituted by C_1-C_6-alkyl, preferably trihalomethyl, C_1-C_6-alkoxy, C_2-C_6-alkenyl, C_2-C_6-alkynyl, amino, aminoacyl, aminocarbonyl, C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfonyl, C_1-C_6-thioalkoxy.

5. A sulfonamide derivative according to claim 4, wherein Ar^1 is an unsubstituted or substituted phenyl and/or Ar^2 is a thienyl group.

6. A sulfonamide derivative according to any of the preceding claims, wherein Ar^1 is a 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl.

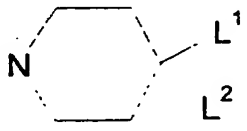
7. A sulfonamide derivative according to any of the preceding claims, wherein Y is



with $(R^6)_n$, L^1 and L^2 being as above defined.

8. Sulfonamide derivatives according to any of the preceding claims, wherein

Ar^1 is 4-chlorophenyl, X is O, R^1 is hydrogen, n is 1, Ar^2 is thienyl, Y is



whereby

L^1 is H, L^2 is a 5-membered cyclic group containing 3 heteroatoms, preferably a triazole ring which is preferably fused with an unsubstituted or substituted aryl or heteroaryl; or L^2 is -C(O)-R^3, or -NHR^3;

with R^3 being a substituent selected from the group comprising or consisting of aryl, heteroaryl, aryl-C_1-C_6-alkyl, heteroaryl-C_1-C_6-alkyl;

said aryl or heteroaryl groups being optionally substituted by halogen, hydroxy, nitro, sulfonyl.

9. A sulfonamide derivative according to any of the preceding claims selected from the following group :

4-Chloro-*N*-[5-(piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-*N*-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide 4-Chloro-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

3-Methoxy-*N*-(5-{4-[1-(4-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-[5-(4-pyrimidin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-pyridin-2-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(1-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-oxo-2-pyrrolidin-1-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-pyridin-4-ylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-thiophen-2-yl-ethyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,5-dimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-cyclohexylmethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(2-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-[5-(4-phenethyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-fluoro-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-cyano-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(chloro-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-piperidin-1-yl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-chloro-2-nitro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(6-methyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-hydroxy-4-phenyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(1-phenyl-methanoyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-[5-(4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]decane-8-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-(5-{4-[(methyl-phenyl-carbamoyl)-methyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-{5-[4-(1-hydroxy-1,1-diphenyl-methyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(3'-Cyano-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(5-Nitro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(Chloro-trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(5-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzotriazol-1-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-(5-{4-[1-(4-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

5-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-7-trifluoromethyl-thieno[3,2-b]pyridine-3-carboxylic acid methyl ester

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-5-cyano-6-methyl-nicotinic acid ethyl ester

4-Chloro-N-{5-[4-(cyano-bis-dimethylamino-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(methyl-trifluoromethyl-quinolin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazine-1-carboxylic acid tert-butyl ester

2-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-8-ethyl-5-oxo-5,8-dihydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

7-{4-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperazin-1-yl}-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

4-Chloro-N-{5-[4-(1-2,3-Dihydro-benzo[1,4]dioxin-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-((E)-3-Phenyl-allyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-phenyl-propyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,4,5-trimethoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-tert-Butyl-benzyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-fluoro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-hydroxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(4-Trifluoromethyl-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(5-cyano-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

{1-[5-({[1-(4-Chloro-phenyl)-methanoyl]-amino}-methyl)-thiophene-2-sulfonyl]-piperidin-4-yl}-carbamide acid tert-butyl ester

4-Chloro-N-[5-(4-phenyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(4-naphthalen-1-yl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(3,4-dichloro-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-trifluoromethyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[3-Hydroxy-4-(3-trifluoromethyl-phenyl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-o-tolyl-piperazine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-((1R,4R)-5-Benzyl-2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-[5-(4-Benzyloxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-{5-[4-(2-Chloro-dibenzo[*b, f*][1,4]oxazepin-11-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

N-(4-Chloro-phenyl)-2-{5-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-sulfonyl]-thiophen-2-yl}-acetamide

4-Chloro-N-[5-(4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(4-Acetyl-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3,5-dichloro-pyridin-4-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(3-methoxy-phenyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-[5-(4-Benzyl-4-hydroxy-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-{5-[4-(2-*tert* butyl-1*H*-indol-5-ylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(2-phenyl-ethanoylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-tetrahydro-furan-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(6-chloro-pyridin-2-yl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-[5-(4-Benzotriazol-2-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-benzamide

4-Chloro-*N*-{5-[4-(5-chloro-benzotriazol-2-yl)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-phenyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-N-(5-{4-[1-(4-chloro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(4-trifluoromethyl-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-*p*-tolyl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(4-dimethylamino-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2,6-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(3-fluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-naphthalen-2-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-{5-[4-(1-naphthalen-1-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(2-nitro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-(1-pyridin-3-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

N-{5-[4-(1-Benzo[1,2,5]oxadiazol-5-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-4-chloro-benzamide

4-Chloro-*N*-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(2,4,6-trifluoro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-{5-[4-((E)-3-phenyl-allanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide

4-Chloro-*N*-(5-{4-[1-(2,6-dichloro-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-*N*-(5-{4-[1-(3,5-dimethoxy-phenyl)-methanoyl]-piperazine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

10. A sulfonamide derivative according to claim 9, which is selected from the group consisting of

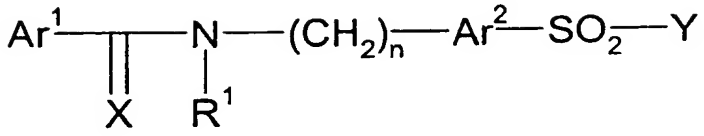
4-Chloro-N-[5-(4-Benzotriazol-1-yl-piperidine-1-sulfonyl)-thiophen-2-ylmethyl]-4-chloro-benzamide

4-Chloro-N-(5-{4-[1-(2,4-difluoro-phenyl)-methanoyl]-piperidine-1-sulfonyl}-thiophen-2-ylmethyl)-benzamide

4-Chloro-N-{5-[4-(3-Trifluoromethanesulfonyl-phenylamino)-piperidine-1-sulfonyl]-thiophen-2-ylmethyl}-benzamide.

N-{5-[4-(1-Benzo[1,2,5]oxadiazol-5-yl-methanoyl)-piperazine-1-sulfonyl]-thiophen-2-ylmethyl}-4-chloro-benzamide.

11. Use of a sulfonamide derivative according to formula I



I

wherein Ar^1 and Ar^2 are independently from each other substituted or unsubstituted aryl or heteroaryl groups;

X is O or S, preferably O;

R^1 is hydrogen or a C_1-C_6-alkyl group, or R^1 forms a substituted or unsubstituted 5-6-membered saturated or unsaturated ring with Ar^1;

n is an integer from 0 to 5, preferably between 1-3 and most preferred 1;

Y within formula I is an unsubstituted or a substituted 4-12-membered saturated cyclic or bicyclic alkyl containing at least one nitrogen atom, whereby one nitrogen atom within said ring is forming a bond with the sulfonyl group of formula I thus providing a sulfonamide,

for the preparation of a pharmaceutical composition for the modulation of the JNK pathway.

12. Use according to claim 11 for the treatment or prevention of disorders associated with the abnormal expression or activity of JNK.

13. Use according to claim 12 for the treatment or prevention of disorders associated with abnormal expression or activity of JNK2 and/or 3.

14. Use according to any of claims 11 to 13 for the treatment of neuronal disorders including epilepsy; Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases, spinal cord injury, head trauma.

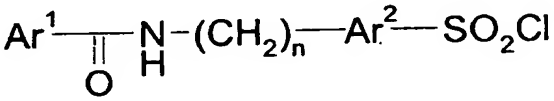
15. Use according to any of claims 11 to 13 for the treatment of autoimmune diseases including Multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis, asthma, septic shock, transplant rejection.

16. Use according to any of claims 11 to 13 for the treatment of cancer including breast-, colorectal-, pancreatic cancer.

17. Use according to any of claims 11 to 13 for the treatment of cardiovascular diseases including stroke, arterosclerosis, myocordial infarction, myocordial reperfusion injury.

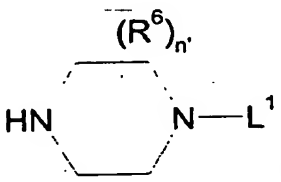
18. A pharmaceutical composition containing at least one sulfonamide derivative according to any of the claims 2 to 10 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

19. Process for the preparation of a sulfonamide derivative according to any of claims 1 to 10, wherein a sulfonyl chloride V

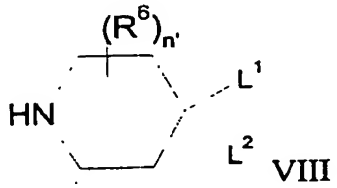


V

is reacted with an amine VII or VIII



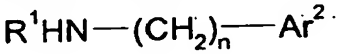
VII or



VIII

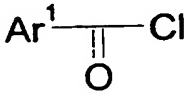
whereby $(R^6)_n$, L^1 and L^2 are as above defined.

20. A process according to claim 19, wherein a sulfonyl chloride V is obtained by a) coupling an amine of formula II:



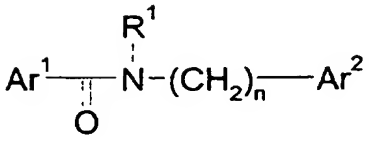
II

where Ar^2 and R^1 are as defined above, with an acyl chloride of formula III:



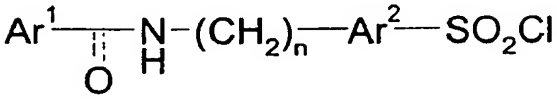
III

where Ar^1 is as defined above, to provide an amide of formula IV:



IV

b) sulfonating the amide of formula IV to provide a sulfonyl chloride V



V

Abstract of the invention

The present invention is related to sulfonamide derivatives notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such sulfonamide derivatives. Said sulfonamide derivatives are efficient modulators of the JNK pathway, they are in particular efficient and selective inhibitors of JNK 2 and 3. The present invention is furthermore related to novel sulfonamide derivatives as well as to methods of their preparation.